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Diastereoselective Synthesis of Bicyclic γ-Lactams via Ring Expansion of Monocyclic β-Lactams

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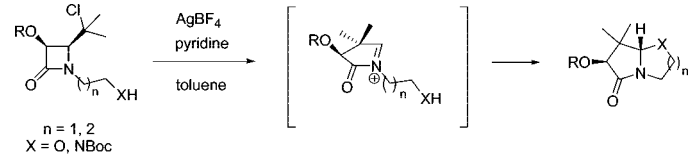

cis-4-(1-Chloro-1-methylethyl)-1-(ω-hydroxyalkyl)azetidin-2-ones were diastereoselectively transformed into novel *trans*-1-aza-4-oxabicyclo[3.3.0]octan-8-ones and *trans*-1-aza-5-oxabicyclo[4.3.0]nonan-9-ones upon treatment with 1 equiv of $AgBF_4$ and pyridine in toluene via intramolecular nucleophilic trapping of *N*-acyliminium intermediates by the hydroxyl moiety. Additionally, the corresponding aza-analogues of the aforementioned bicyclic γ-lactams (i.e., *trans*-1,4-diazabicyclo[3.3.0]octan-8-ones and *trans*-1,5-diazabicyclo[4.3.0]nonan-9-ones) were prepared in a convenient way starting from *cis*-4-(1-chloro-1-methylethyl)-1-{ω-[(*tert*-butoxycarbonyl)amino]alkyl}azetidin-2-ones applying the same reaction conditions. The intermediate *N*-acyliminium ions were formed by ring expansion of the starting β-lactams through generation of a transient silver(I)-induced carbenium ion.

Introduction

Because of their interesting biological properties, functionalized bicyclic γ-lactams receive considerable attention nowadays from a medicinal point of view. As bacterial resistance toward traditional β-lactam antibiotics increases rapidly, bicyclic γ-lactams, such as penem analogues, provide a useful alternative as antibacterial compounds due to their structural similarity with bicyclic β-lactams.[1] Substituted with the appropriate functional groups, bicyclic γ-lactams, for example, thiazolidine derivatives, can also imitate the conformation of a β-turn and thus act as peptidomimetics.[2] Furthermore, some bicyclic γ-lactams, such as 1-aza-4-thia-7-amino-2-cyanobicyclo[3.3.0]octan-8-ones, are applied in medicine for the treatment of type 2 diabetes.[3]

1-Azabicyclo[3.3.0]octan-8-ones **1a** and 1-azabicyclo[4.3.0]-nonan-9-ones **1b** comprise two biologically important representatives of bicyclic γ-lactams and are generally synthesized via two different entries, either via cyclocondensation reactions of β-amino alcohols/thiols with γ-keto acids/esters[2b,d,3a,4] or via acid-catalyzed cyclizations starting from monocyclic γ-lactams via *N*-acyliminium intermediates.[5] Other synthetic routes toward these types of bicyclic γ-lactams include radical-mediated cyclizations of norephedrine-derived α-iodoamides,[6] electrophile-induced cyclizations of 5-(halomethyl)pyrrolidin-2-ones,[7] and syntheses of γ-lactam analogues of β-lactam antibiotics

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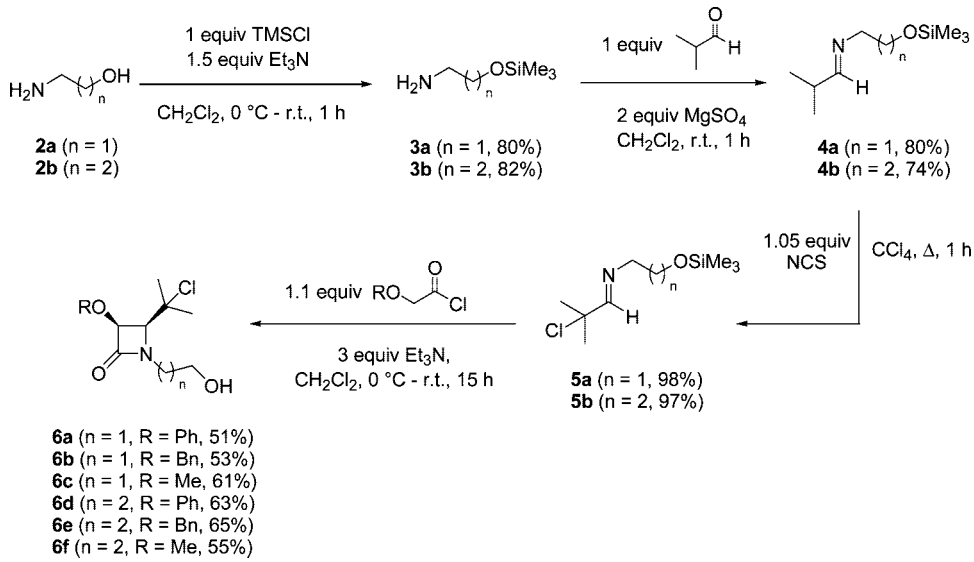
SCHEME 1



which comprise cleavage of the amide bond and subsequent ring closure via UV radiation.[8]

1a **1b**

X = O, N, S

To date, only one peculiar example of a ring expansion of a monocyclic β-lactam toward a bicyclic γ-lactam via a *N*-acyliminium ion has been reported, in which the *N*-acyliminium intermediate is generated through epoxidation of a propenyl group at C4 in acidic medium.[9] However, the formation of epoxides as byproducts can be considered as a serious drawback for the presented synthetic route.

Encouraged by previous results on the diastereoselective ring expansion of β-lactams toward monocyclic pyrrolidin-2-ones,[10] a new ring transformation of *cis*-4-(1-chloro-1-methylethyl)azetidin-2-ones into novel bicyclic γ-lactams via intramolecular nucleophilic trapping of *N*-acyliminium intermediates is disclosed in the present paper. This is the first report on the full conversion of monocyclic β-lactams into bicyclic γ-lactams via *N*-acyliminium ions. It should be noted that recently a similar rearrangement of 4-formyl-β-lactams into monocyclic γ-lactams through reaction with tributylsilyl cyanide and iodine has been reported.[11] In this case, however, the driving cationic intermediate was generated via Lewis acid catalysis.

Results and Discussion

In order to circumvent difficulties associated with the presence of a free hydroxyl group in aminoalcohols **2** during β-lactam formation, 2-aminoethanol **2a** and 3-amino-1-propanol **2b** were first protected as their trimethylsilyl ethers **3a**,**b** using a slightly modified literature procedure, involving treatment with 1 equiv of TMSCl and 1.5 equiv of Et_3N in dichloromethane at room temperature for 1 h.[12] Subsequent imination of isobutyraldehyde with amines **3** in dichloromethane in the presence of $MgSO_4$ as drying agent led to the formation of (*E*)-*N*-(2-methylpropylidene)amines **4a**,**b**, which then underwent α-chlorination with respect to the imino bond using 1.05 equiv of *N*-chlorosuccinimide (NCS) in CCl_4 to give the chlorinated imines **5a**,**b** in almost quantitative yields after reflux for 1 h (Scheme 1).[13] Subsequently, α-chloroimines **5** were used as substrates for the Staudinger reaction upon treatment with 1.1 equiv of three different acid chlorides (i.e., phenoxy-, benzyloxy-, and methoxyacetyl chloride) in the presence of triethylamine in dichloromethane, affording the corresponding novel 4-(1-chloro-1-methylethyl)-1-(ω-hydroxyalkyl)azetidin-2-ones **6a**−**f** after 15 h at room temperature (Scheme 1). This reaction concerns the [2 + 2] cycloaddition of imines **5** with the ketenes generated from the phenoxy- and alkoxyacetyl chlorides. It has to be remarked that the reported yields are those obtained after purification by column chromatography. It should be noted that, during column chromatography, removal of the trimethylsilyl group at oxygen took place, making a deprotection step unnecessary. The relative stereochemistry of β-lactams **6** was assigned as *cis* based on the coupling constants between the protons at C3 and C4 in ^1H NMR (5.1−5.3 Hz, $CDCl_3$), in accordance with literature data.[14,15]

Upon treatment with 1 equiv of $AgBF_4$ and 1 equiv of pyridine in toluene under reflux for 15 h, *cis*-4-(1-chloro-1-methylethyl)-1-(2-hydroxyethyl)azetidin-2-ones **6a**−**c** were converted into a mixture of novel *trans*- and *cis*-1-aza-4-oxa-7-alkoxy-6,6-dimethylbicyclo[3.3.0]octan-8-ones **7** and **8** (Scheme 2). Applying the same reaction conditions, *cis*-4-(1-chloro-1-methylethyl)-1-(3-hydroxypropyl)azetidin-2-ones **6d**−**f** were also transformed into a mixture of novel *trans*- and *cis*-1-aza-

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SCHEME 2

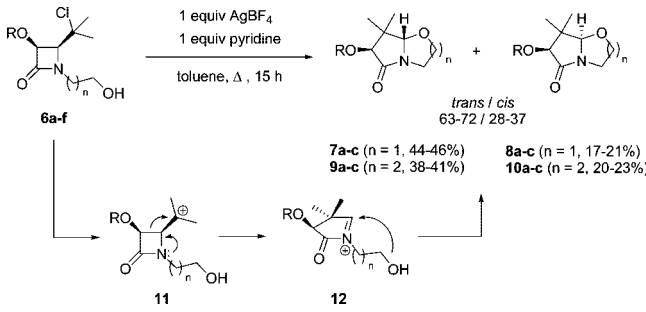


TABLE 1. Synthesis of *cis*- and *trans*-Bicyclic γ-Lactams 7−10

compound	R	isolated yield (%)[a]	ratio **7**/**8**[b]	compound	R	isolated yield (%)[a]	ratio **9**/**10**[b]
7a	Ph	44	66/34	**9a**	Ph	39	63/37
8a	Ph	21		**10a**	Ph	23	
7b	Bn	46	72/28	**9b**	Bn	41	66/34
8b	Bn	18		**10b**	Bn	21	
7c	Me	45	70/30	**9c**	Me	38	66/34
8c	Me	17		**10c**	Me	20	

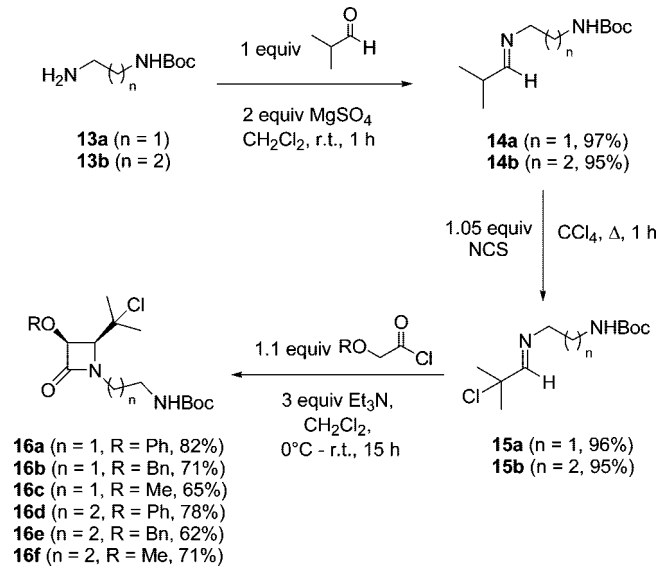
[a] After purification by column chromatography on silica gel. [b] Based on ^{1}H NMR and/or GC of the crude reaction mixture.

5-oxa-8-alkoxy-7,7-dimethylbicyclo[4.3.0]nonan-9-ones **9** and **10** (Scheme 2 and Table 1). This new ring transformation of monocyclic β-lactams into bicyclic γ-lactams appeared to be diastereoselective, as the *trans* isomers **7** and **9** were formed as the major constituents (*trans*/*cis* 63−72/28−37). In all cases, both the major and minor compounds **7**−**10** could be isolated in pure form by means of column chromatography on silica gel.

In the case of 1-aza-5-oxabicyclo[4.3.0]nonan-9-ones **9** and **10**, the stereochemistry of the two diastereomers was unambiguously determined based on the appearance of a W coupling in ^{1}H NMR (0.8−1.1 Hz, $CDCl_3$) between the protons at C6 and C8 on the bicyclic γ-lactam ring, which is known to be characteristic for the *cis* isomers.[10,16] Unfortunately, no W coupling was observed in the ^{1}H NMR spectrum ($CDCl_3$) of compounds **8**. In these cases, the stereochemistry was assigned based on the δ values of the geminal dimethyl group at C6 in ^{13}C NMR ($CDCl_3$). In γ-lactams **10**, where the *cis* stereochemistry was determined based on the presence of a W coupling, the difference between the δ values for the two methyl groups was approximately 10 ppm ($CDCl_3$), whereas the two CH_3 signals in ^{13}C NMR ($CDCl_3$) of the *trans* derivatives **9** appeared very close to each other ($\Delta\delta$ < 0.5 ppm, $CDCl_3$). The same observations were made for *trans*- and *cis*-1-aza-4-oxa-7-alkoxy-6,6-dimethylbicyclo[3.3.0]octan-8-ones **7** and **8**, enabling the correct stereochemical assignment.

The conversion of *cis*-4-(1-chloro-1-methylethyl)-1-(ω-hydroxyalkyl)azetidin-2-ones **6** into 1-aza-4-oxabicyclo[3.3.0]octan-8-ones **7** and **8** and 1-aza-5-oxabicyclo[4.3.0]nonan-9-ones **9** and **10** proceeds through $AgBF_4$-mediated dissociation of the chloro atom, driven by the precipitation of the resulting silver chloride. Addition of $AgBF_4$ proved to be necessary for the reaction, as attempts without the silver salt turned out to be unsuccessful (recovery of starting material). The halide dissociation leads to the formation of tertiary carbenium ions **11**, which initiate an intramolecular rearrangement via opening of the C3−C4 bond toward the formation of *N*-acyliminium ions **12** (Scheme 2).[10] Subsequently, intramolecular trapping by the free hydroxyl group takes place, resulting in the formation of bicyclic γ-lactams **7**−**10** (Scheme 2). The observed diastereoselectivity can be rationalized considering the sterical hindrance of the phenoxy or alkoxy substituent of the *N*-acyliminium moiety in intermediates **12**. Therefore, the attack of the hydroxyl group is favored at the opposite side of the alkoxy substituent, resulting in *trans* isomers **7** and **9** as the major compounds. On the other hand, the ether group at the top face can have a conformational effect on the five-membered ring, thereby reducing the directing effect of the top face ether.

SCHEME 3



Apart from the isolated report mentioned above,[9] this approach comprises the first general transformation of monocyclic β-lactams into bicyclic γ-lactams via *N*-acyliminium intermediates and illustrates the great synthetic potential of *cis*-4-(1-haloalkyl)azetidin-2-ones in organic chemistry.[10,15]

In order to extend the scope of the study, the synthesis of the aza-analogues of the latter bicyclic γ-lactams **7**−**10** was envisaged. Therefore, two commercially available *N*-Boc-protected diamines **13a** and **13b** were condensed with 1 equiv of isobutyraldehyde in dichloromethane in the presence of $MgSO_4$ to give imines **14a**,**b** (95−97% yield) which were transformed into (*E*)-*N*-(2-chloro-2-methylpropylidene)amines **15a**,**b** upon chlorination with 1.05 equiv of *N*-chlorosuccinimide in CCl_4 (Scheme 3). Then a Staudinger reaction using 1.1 equiv of phenoxy-, benzyloxy-, and methoxyacetyl chloride in dichloromethane was performed, affording the corresponding novel 3-alkoxy-4-(1-chloro-1-methylethyl)azetidin-2-ones **16a**−**f** in good yields (Scheme 3). Also for β-lactams **16**, the relative stereochemistry was determined as *cis*, in accordance with literature data.[14,15]

Applying the same reaction conditions as mentioned above (i.e., 1 equiv of $AgBF_4$ and 1 equiv of pyridine in toluene under reflux for 15 h), azetidin-2-ones **16a**−**f** were converted to the corresponding novel 1,4-diaza-7-alkoxy-6,6-dimethyl-4-(*tert*-butoxycarbonyl)bicyclo[3.3.0]octan-8-ones **17** and **18** and 1,4-diaza-8-alkoxy-7,7-dimethyl-5-(*tert*-butoxycarbonyl)bicyclo[4.3.0]-nonan-9-ones **19** and **20** in moderate yields (Scheme 4 and Table 2). Again, the relative stereochemistry of the two diastereomers

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SCHEME 4

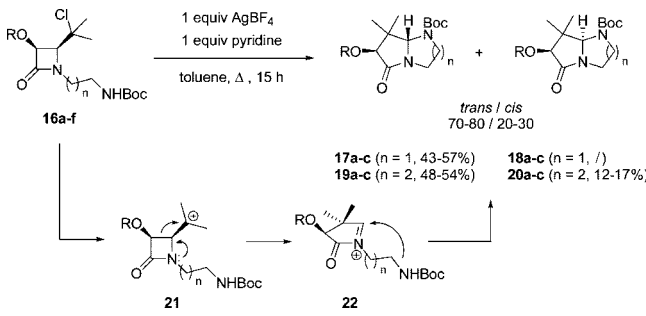

TABLE 2. Synthesis of *cis*- and *trans*-Bicyclic γ-Lactams 17−20

compound	R	isolated yield (%)[a]	ratio **17/18**[b]	compound	R	isolated yield (%)[a]	ratio **19/20**[b]
17a	Ph	53	77/23	**19a**	Ph	54	70/30
18a	Ph	-[c]		**20a**	Ph	17	
17b	Bn	57	70/30	**19b**	Bn	48	80/20
18b	Bn	-[c]		**20b**	Bn	-[c]	
17c	Me	43	71/29	**19c**	Me	51	80/20
18c	Me	-[c]		**20c**	Me	12	

[a] After purification by column chromatography on silica gel. [b] Based on ^{1}H NMR and/or GC of the crude reaction mixture. [c] The minor isomer could not be isolated by column chromatography.

could be assigned based on the δ values of the geminal dimethyl group at C6 and C7 in ^{13}C NMR ($CDCl_3$): for the *trans* isomers **17** and **19**, the two CH_3 signals in ^{13}C NMR ($CDCl_3$) appeared very close to each other ($\Delta\delta$ < 1 ppm, $CDCl_3$), whereas for the *cis* derivatives **20** a difference of approximately 10 ppm ($CDCl_3$) between the δ values for the two methyl groups was observed. In correspondence with the oxa analogues, the *trans* derivatives **17** and **19** were formed as the major compounds, pointing to a diastereoselective process. These *trans*-1,4-diazabicyclo[3.3.0]octan-8-ones **17** and *trans*-1,5-diazabicyclo[4.3.0]-nonan-9-ones **19** could also be isolated in pure form by means of column chromatography on silica gel. In general, a higher degree of diastereoselectivity was observed for 1,4-diazabicyclo[3.3.0]octan-8-ones and 1,5-diazabicyclo[4.3.0]nonan-9-ones **17**−**20** in comparison with 1-aza-4-oxabicyclo[3.3.0]octan-8-ones and 1-aza-5-oxabicyclo[4.3.0]nonan-9-ones **7**−**10**. The presence of a bulky Boc group can account for these observations, resulting in more steric hindrance with the alkoxy group during the cyclization process.

Conclusions

In summary, *cis*-4-(1-chloro-1-methylethyl)-1-(ω-hydroxyalkyl)azetidin-2-ones proved to be useful starting materials for a novel and efficient diastereoselective synthesis of *trans*-1-aza-4-oxabicyclo[3.3.0]octan-8-ones and *trans*-1-aza-5-oxabicyclo[4.3.0]nonan-9-ones via a ring transformation protocol using $AgBF_4$ and pyridine in toluene. In addition, the aza-analogues *trans*-1,4-diazabicyclo[3.3.0]octan-8-ones and *trans*-1,5-diazabicyclo[4.3.0]nonan-9-ones were prepared using an analogous approach. This is the first report on the full conversion of monocyclic β-lactams into bicyclic γ-lactams via *N*-acyliminium intermediates.

Experimental Section

Synthesis of (*E*)-*N*-(2-Methylpropylidene)amines 4 and 14. As a representative example, the synthesis of (*E*)-*N*-(2-methylpropylidene)-2-(trimethylsilyloxy)ethylamine **4a** is described.

To a solution of 2-(trimethylsilyloxy)ethylamine **3a** (13.9 mmol) in anhydrous CH_2Cl_2 (50 mL) were added $MgSO_4$ (27.8 mmol, 2 equiv) and isobutyraldehyde (13.9 mmol, 1 equiv). After stirring for 1 h at room temperature, $MgSO_4$ was removed by filtration. After evaporation of the solvent, (*E*)-*N*-(2-methylpropylidene)-2-(trimethylsilyloxy)ethylamine **4a** was obtained in 80% yield.

Imines **4** and **14** were obtained in high purity (>95%) and used as such in the next reaction step due to their hydrolytic instability.

(*E*)-*N*-(2-Methylpropylidene)-2-(trimethylsilyloxy)ethylamine 4a: Colorless liquid; yield 80% (purity 95%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.10 (9H, s), 1.08 (6H, d, J = 6.9 Hz), 2.36−2.49 (1H, m), 3.48 (2H, t, J = 5.9 Hz), 3.66 (2H, t, J = 5.9 Hz), 7.53 (1H, d × t, J = 5.0, 1.1 Hz); ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ −0.3 (CH_3), 19.4 (CH_3), 34.2 (CH), 62.1 (CH_2), 63.2 (CH_2), 171.8 (C); IR (NaCl, cm^{-1}) $\nu_{C=N}$ = 1673; ν_{max} = 2959, 2870, 1467, 1250, 1106, 839, 748; MS (70 eV) *m*/*z* (%) 188 (M^+ + 1, 48), 134 (100).

(*E*)-*N*-(2-Methylpropylidene)-2-[(*tert*-butoxycarbonyl)amino]ethylamine 14a: Colorless liquid; yield 97% (purity 98%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (6H, d, J = 6.9 Hz), 1.44 (9H, s), 2.38−2.48 (1H, m), 3.31−3.36 (2H, m), 3.45 (2H, t, J = 5.5 Hz), 4.76 (1H, br s), 7.55 (1H, d, J = 5.0 Hz); ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 19.4 (CH_3), 28.5 (CH_3), 34.2 (CH), 41.3 (CH_2), 60.5 (CH_2), 77.3 (C), 156.0 (C), 172.0 (C); IR (NaCl, cm^{-1}) ν_{NH} = 3348; $\nu_{C=O}$ = 1695; $\nu_{C=N}$ = 1671; ν_{max} = 2967, 1518, 1365, 1270, 1250, 1169, 867, 780; MS (70 eV) *m*/*z* (%) 216 (M^+ + 1, 27), 162 (100).

Synthesis of (*E*)-*N*-(2-Chloro-2-methylpropylidene)amines 5 and 15. As a representative example, the synthesis of (*E*)-*N*-(2-chloro-2-methylpropylidene)-2-(trimethylsilyloxy)ethylamine **5a** is described.

N-Chlorosuccinimide (10.6 mmol, 1.05 equiv) was added to a solution of (*E*)-*N*-(2-methylpropylidene)-2-(trimethylsilyloxy)ethylamine **4a** (10.1 mmol, 1 equiv) in CCl_4 (50 mL). The resulting mixture was refluxed for 1 h, after which the reaction mixture was placed in the freezer (1 h). After removal of the succinimide by filtration and evaporation of the solvent, (*E*)-*N*-(2-chloro-2-methylpropylidene)-2-(trimethylsilyloxy)ethylamine **5a** was obtained in 98% yield.

Imines **5** and **15** were obtained in high purity (>90%) and used as such in the next reaction step due to their hydrolytic instability.

(*E*)-*N*-(2-Chloro-2-methylpropylidene)-2-(trimethylsilyloxy)ethylamine 5a: Light-yellow liquid; yield 98% (purity 94%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.10 (9H, s), 1.70 (6H, s), 3.56 (2H, t × d, J = 5.5, 1.0 Hz), 3.79 (2H, t, J = 5.5 Hz), 7.69 (1H, t, J = 1.0 Hz); ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ −0.4 (CH_3), 29.4 (CH_3), 61.6 and 62.2 (2 × CH_2), 68.0 (C), 166.9 (C); IR (NaCl, cm^{-1}) $\nu_{C=N}$ = 1670; ν_{max} = 2957, 2870, 1250, 1114, 1097, 838, 748; MS (70 eV) *m*/*z* (%) 222/4 (M^+ + 1, 100).

(*E*)-*N*-(2-Chloro-2-methylpropylidene)-2-[(*tert*-butoxycarbonyl)-amino]ethylamine 15a: Light-yellow liquid; yield 96% (purity 91%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (9H, s), 1.70 (6H, s), 3.34−3.39 (2H, m), 3.54 (2H, t, J = 5.5 Hz), 4.74 (1H, br s), 7.71 (1H, s); ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 28.3 (CH_3), 29.1 and 29.5 (CH_3), 40.6 (CH_2), 59.1 (CH_2), 67.6 (C), 78.6 (C), 155.7 (C), 166.3 (C); IR (NaCl, cm^{-1}) ν_{NH} = 3346; $\nu_{C=O}$ and $\nu_{C=N}$ = 1696; ν_{max} = 2977, 1512, 1366, 1271, 1250, 1168, 1115, 783; MS (70 eV) *m*/*z* (%) 249/51 (M^+ + 1, 100).

Synthesis of *cis*-3-Alkoxy-4-(1-chloro-1-methylethyl)azetidin-2-ones 6 and 16. As a representative example, the synthesis of *cis*-4-(1-chloro-1-methylethyl)-1-(2-hydroxyethyl)-3-phenoxyazetidin-2-one **6a** is described.

To a solution of (*E*)-*N*-(2-chloro-2-methylpropylidene)-2-(trimethylsilyloxy)ethylamine **5a** (3.6 mmol, 1 equiv) and Et_3N (10.8 mmol, 3 equiv) in anhydrous CH_2Cl_2 (25 mL) was added dropwise a solution of phenoxyacetyl chloride (4 mmol, 1.1 equiv) in anhydrous CH_2Cl_2 (10 mL). The reaction mixture was stirred for 15 h at room temperature and then washed with water (25 mL). Subsequently, the aqueous phase was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic fractions were dried over $MgSO_4$. After filtration of the drying agent and evaporation of the solvent, the crude reaction mixture was obtained. Further purification was

performed by column chromatography (hexane/EtOAc 1/1, R_f = 0.11), affording *cis*-4-(1-chloro-1-methylethyl)-1-(2-hydroxyethyl)-3-phenoxyazetidin-2-one **6a** in 63% yield.

***cis*-4-(1-Chloro-1-methylethyl)-1-(2-hydroxyethyl)-3-phenoxyazetidin-2-one 6a:** White crystals; mp 121.1 °C; R_f = 0.11 (hexane/EtOAc 1/1); yield 63% (crude 90%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.78 and 1.84 (2 × 3H, 2 × s), 3.39 (1H, br s), 3.48 and 3.80 (2 × 1H, 2 × (d × t), J = 14.7, 4.9 Hz), 3.94 (2H, t, J = 4.9 Hz), 4.28 (1H, d, J = 5.1 Hz), 5.30 (1H, d, J = 5.1 Hz), 7.02−7.11 and 7.28−7.35 (3H and 2H, 2 × m); ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 27.4 and 29.7 (2 × CH_3), 47.6 (CH_2), 59.8 (CH_2), 67.9 (CH), 71.3 (C), 80.2 (CH), 116.0 (2 × CH), 122.9 (CH), 129.8 (2 × CH), 157.5 (C), 168.0 (C); IR (KBr, cm^{-1}) ν_{OH} = 3391−3333; $\nu_{C=O}$ = 1721; ν_{max} =2928, 1492, 1236, 1106, 1056, 768, 748, 692; MS (70 eV) *m*/*z* (%) 284/6 (M^+ + 1, 100). Anal. Calcd for $C_{14}H_{18}ClNO_3$: C, 59.26; H, 6.39; N, 4.94. Found: C, 59.47; H, 6.68; N, 4.71.

***cis*-4-(1-Chloro-1-methylethyl)-3-phenoxy-1-{2-[(*tert*-butoxycarbonyl)amino]ethyl}-azetidin-2-one 16a:** Yellow crystals; mp 107.9 °C; R_f = 0.18 (hexane/EtOAc 9/2); yield 82%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (9H, s), 1.77 and 1.81 (2 × 3H, 2 × s), 3.15−3.19, 3.45−3.51, and 3.64−3.81 (1H, 1H, and 2H, 3 × m), 4.51 (1H, d, J = 5.3 Hz), 4.95 (1H, br s), 5.19 (1H, d, J = 5.3 Hz), 6.98−7.08 and 7.27−7.32 (3H and 2H, 2 × m); ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 27.4 and 29.7 (2 × CH_3), 28.48 (CH_3), 37.8 and 43.2 (2 × CH_2), 66.7 (CH), 71.7 (C), 79.7 (C), 80.8 (CH), 115.9 (2 × CH), 122.7 (CH), 129.7 (2 × CH), 156.3 (C), 157.7 (C), 167.7 (C); IR (KBr, cm^{-1}) ν_{NH} = 3431; $\nu_{NC=O}$ = 1750; $\nu_{NHC=O}$ = 1692; ν_{max} = 2970, 1518, 1495, 1237, 1171, 750, 691; MS (70 eV) *m*/*z* (%) no M^+; 283/5 (100). Anal. Calcd for $C_{19}H_{27}ClN_2O_4$: C, 59.60; H, 7.11; N, 7.32. Found: C, 59.66; H, 7.46; N, 7.26.

Synthesis of Bicyclic γ-Lactams 7−10 and 17−20. As a representative example, the synthesis of *trans*- and *cis*-1-aza-4-oxa-6,6-dimethyl-7-phenoxybicyclo[3.3.0]octan-8-one **7a** and **8a** is described.

cis-4-(1-Chloro-1-methylethyl)-1-(2-hydroxyethyl)-3-phenoxyazetidin-2-one **6a** (0.96 mmol, 1 equiv) was dissolved in anhydrous toluene (25 mL). Then pyridine (0.96 mmol, 1 equiv) and $AgBF_4$ (0.96 mmol, 1 equiv) were added, and the resulting mixture was refluxed for 15 h. Subsequently, toluene was removed by evaporation, and the reaction mixture was re-dissolved in CH_2Cl_2 (25 mL). The reaction mixture was washed with water (25 mL), and the aqueous phase was extracted with CH_2Cl_2 (3 × 25 mL). Drying over $MgSO_4$, removal of the drying agent by filtration, and evaporation of the solvent afforded 1-aza-4-oxa-6,6-dimethyl-7-phenoxybicyclo[3.3.0]octan-8-one as a mixture of *cis*/*trans* isomers. Both isomers **7a** and **8a** were separated by means of column chromatography on silica gel (hexane/EtOAc 2/1).

***trans*-1-Aza-4-oxa-6,6-dimethyl-7-phenoxybicyclo[3.3.0]octan-8-one 7a:** Light-yellow oil; yield 44%; R_f = 0.33 (hexane/EtOAc 2/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 and 1.32 (2 × 3H, 2 × s); 3.20 (1H, d × d × d, J = 10.9, 7.2, 6.1 Hz), 3.83 (1H, d × d × d, J = 10.9, 7.3, 5.9 Hz), 4.03−4.15 (2H, m), 4.36 (1H, s), 5.07 (1H, s), 6.96−7.01, 7.12−7.16, and 7.24−7.31 (1H, 2H, and 2H, 3 × m); ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 19.6 and 19.8 (2 × CH_3), 41.6 (CH_2), 43.2 (C), 68.3 (CH_2), 88.0 (CH), 97.6 (CH), 116.2 (2 × CH), 122.1 (CH), 129.6 (2 × CH), 158.6 (C), 173.7 (C); IR (NaCl, cm^{-1}) $\nu_{C=O}$ = 1713; ν_{max} = 2964, 2890, 1596, 1493, 1228, 1058, 754, 691; MS (70 eV) *m*/*z* (%) 248 (M^+ + 1, 100). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.17; H, 7.14; N, 5.51.

***cis*-1-Aza-4-oxa-6,6-dimethyl-7-phenoxybicyclo[3.3.0]octan-8-one 8a:** Colorless oil; yield 21%; R_f = 0.14 (hexane/EtOAc 2/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 and 1.32 (2 × 3H, 2 × s), 3.11−3.19 and 3.85−3.92 (2 × 1H, 2 × m), 4.00−4.05 (2H, m), 4.74 and 4.86 (2 × 1H, 2 × s), 6.96−7.07 and 7.24−7.30 (3H and 2H, 2 × m); ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 14.96 and 24.04 (2 × CH_3), 41.3 (CH_2), 47.1 (C), 67.1 (CH_2), 85.1 (CH), 94.8 (CH), 116.6 (2 × CH), 122.2 (CH), 129.5 (2 × CH), 159.1 (C), 172.4 (C); IR (NaCl, cm^{-1}) $\nu_{C=O}$ = 1718; ν_{max} = 2922, 1597, 1493, 1229, 1062, 754, 691; MS (70 eV) *m*/*z* (%) 248 (M^+ + 1, 100). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.21; H, 7.19; N, 5.45.

***trans*-1-Aza-5-oxa-7,7-dimethyl-8-phenoxybicyclo[4.3.0]nonan-9-one 9a:** Light-yellow oil; R_f = 0.41 (hexane/EtOAc 1/1); yield 39%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17 and 1.20 (2 × 3H, 2 × s), 1.47−1.52 and 1.73−1.89 (2 × 1H, 2 × m), 3.06 (1H, t × d, J = 12.8, 3.9 Hz), 3.70 (1H, t × d, J = 12.3, 2.1 Hz), 4.11−4.25 (2H, m), 4.50 (1H, s), 4.60 (1H, s), 6.96−7.01, 7.11−7.14, and 7.25−7.31 (1H, 2H, and 2H, 3 × m); ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 20.7 and 20.9 (2 × CH_3), 24.8 (CH_2), 39.5 (CH_2), 41.0 (C), 67.4 (CH_2), 83.2 (CH), 92.6 (CH), 116.7 (2 × CH), 122.0 (CH), 129.5 (2 × CH), 159.3 (C), 171.2 (C); IR (NaCl, cm^{-1}) $\nu_{C=O}$ = 1706; ν_{max} = 2967, 2873, 1597, 1493, 1261, 1231, 1050, 754, 692; MS (70 eV) *m*/*z* (%) 262 (M^+ + 1, 100). Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.07; H, 7.49; N, 5.15.

***cis*-1-Aza-5-oxa-7,7-dimethyl-8-phenoxybicyclo[4.3.0]nonan-9-one 10a:** Colorless oil; R_f = 0.21 (hexane/EtOAc 1/1); yield 23%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 and 1.25 (2 × 3H, 2 × s), 1.54−1.59 and 1.81−1.98 (2 × 1H, 2 × m), 2.99 (1H, t × d, J = 12.8, 3.8 Hz), 3.68 (1H, t × d, J = 12.2, 2.0 Hz), 4.16−4.27 (2H, m), 4.40 (1H, d, J = 0.8 Hz), 4.48 (1H, s), 6.96−7.06 (1H, m), 7.13 (2H, d, J = 7.7 Hz), 7.25−7.30 (2H, m); ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 16.1 and 25.3 (2 × CH_3), 24.4 (CH_2), 38.4 (CH_2), 41.9 (C), 67.1 (CH_2), 83.1 (CH), 91.5 (CH), 116.8 (2 × CH), 122.1 (CH), 129.5 (2 × CH), 159.5 (C), 169.8 (C); IR (NaCl, cm^{-1}) $\nu_{C=O}$ = 1705; ν_{max} = 2964, 2866, 1597, 1491, 1230, 1070, 754, 691; MS (70 eV) *m*/*z* (%) 262 (M^+ + 1, 100). Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.11; H, 7.52; N, 5.12.

***trans*-1,4-Diaza-6,6-dimethyl-7-phenoxy-4-(*tert*-butoxycarbonyl)-bicyclo[3.3.0]octan-8-one 17a:** Light-yellow oil; yield 51%; R_f = 0.19 (hexane/EtOAc 4/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 and 1.44 (2 × 3H, s and br s), 1.52 (9H, s), 3.03−3.09 and 3.16−3.19 (2 × 1H, 2 × m), 3.99−4.05 (2H, m), 4.23 (1H, s), 5.34 (1H, s), 6.94−7.00, 7.15−7.18, and 7.25−7.30 (1H, 2H, and 2H, 3 × m); ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 19.4 and 20.3 (2 × CH_3), 28.5 (CH_3), 40.5 (CH_2), 46.0 and 46.1 (C and CH_2), 80.5 (CH), 81.5 (C), 87.8 (CH), 116.2 (2 × CH), 122.0 (CH), 129.6 (2 × CH), 153.6 (C), 158.5 (C), 171.8 (C); IR (NaCl, cm^{-1}) $\nu_{C=O}$= 1696; ν_{max}= 2976, 1394, 1368, 1229, 1164, 1128, 754, 731; MS (70 eV) *m*/*z* (%) 267 (100). Anal. Calcd for $C_{19}H_{26}N_2O_4$: C, 65.87; H, 7.56; N, 8.09. Found: C, 66.03; H, 7.79; N, 7.96.

***trans*-1,5-Diaza-7,7-dimethyl-8-phenoxy-5-(*tert*-butoxycarbonyl)-bicyclo[4.3.0]nonan-9-one 19a:** White crystals; mp 116.3 °C; yield 54%; R_f = 0.25 (hexane/EtOAc 2/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12 and 1.31 (2 × 3H, 2 × s), 1.51 (9H, s), 1.83−1.95 (2H, m), 2.69−2.80 and 2.93−3.02 (2 × 1H, 2 × m), 4.05−4.25 (2H, m), 4.38 (1H, s), 5.36 (1H, s), 6.93−7.03, 7.17−7.20, and 7.25−7.31 (1H, 2H, and 2H, 3 × m); ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 21.1 and 21.5 (2 × CH_3), 22.4 (CH_2), 28.5 (CH_3), 34.7 and 38.1 (2 × CH_2), 43.4 (C), 76.1 (CH), 81.2 (C), 83.6 (CH), 116.5 (2 × CH), 122.0 (CH), 129.5 (2 × CH), 154.9 (C), 159.0 (C), 170.6 (C); IR (KBr, cm^{-1}) $\nu_{C=O}$= 1715 and 1693; ν_{max}= 2973, 1379, 1368, 1230, 1164, 1131, 1062, 753, 694; MS (70 eV) *m*/*z* (%) 361 (M^+ + 1, 100). Anal. Calcd for $C_{20}H_{28}N_2O_4$: C, 66.64; H, 7.83; N, 7.77. Found: C, 67.02; H, 8.10; N, 7.66.

***cis*-1,5-Diaza-7,7-dimethyl-8-phenoxy-5-(*tert*-butoxycarbonyl)-bicyclo[4.3.0]nonan-9-one 20a:** Colorless oil; yield 17%; R_f = 0.16 (hexane/EtOAc 2/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.11 and 1.32 (2 × 3H, 2 × s), 1.51 (9H, s), 1.85−1.95 (2H, m), 2.88−2.99 (2H, m), 4.03−4.08 and 4.15−4.25 (2 × 1H, 2 × m), 4.48 (1H, d, J = 0.8 Hz), 5.22 (1H, s), 6.97−7.02, 7.10−7.13, and 7.24−7.31 (1H, 2H, and 2H, 3 × m); ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 16.4 and 26.3 (2 × CH_3), 22.5 (CH_2), 28.5 (CH_3), 34.4 and 37.6 (2 × CH_2), 45.2 (C), 75.0 (CH), 81.1 (C), 83.2 (CH), 116.7 (2 × CH), 122.1 (CH), 129.5 (2 × CH), 154.8 (C), 159.4 (C), 170.7 (C); IR (NaCl, cm^{-1}) $\nu_{C=O}$ = 1714 and 1693; ν_{max}= 2972, 1377, 1368, 1229, 1162,

1131, 1062, 752, 693; MS (70 eV) *m*/*z* (%) 361 ($M^+ + 1$, 100). Anal. Calcd for $C_{20}H_{28}N_2O_4$: C, 66.64; H, 7.83; N, 7.77. Found: C, 66.99; H, 8.14; N, 7.56.

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Supporting Information Available: Spectroscopic data of compounds **4b**, **14b**, **5b**, **15b**, **6b**−**f**, **16b**−**f**, **7b**,**c**, **8b**,**c**, **9b**,**c**, **10b**,**c**, **17b**,**c**, **19b**,**c**, **20c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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